Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 117-121, 123-126, 128-135, 137-140, and 142-147 are pending in the application, with 117 and 131 as the independent claims. Claims 122, 127, 136, 141, and 148-213 have been canceled, and claims 119, 120, 123, 125, 126, 128, 133, 134, 137, 139, 140, and 142 have been amended. Applicants reserve the right to pursue the canceled subject matter in a continuing application.

Claims 119, 120, 125, 126, 133, 134, 139, and 140 have been amended to cancel the terms "Avian Sarcoma-Leukosis Virus (ASLV)" and "ASLV." The amendment does not narrow the scope of the claims. Support for the amendment may be found in the specification, for example, at page 3, line 27 to page 4, line 5.

It is believed that these changes introduce no new matter, and their entry is respectfully requested. Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and request that they be withdrawn.

Interview

Applicants thank Examiner Nashed for the courteous and helpful interview extended to Applicants' representatives Robert Esmond and Helene Carlson on April 7, 2003.

The Sequence Listing

The Office Action, at page 2, maintained that the present application is not in compliance with the sequence rules. The concern expressed in the Office Action is that the specification describes mutations at several specific positions in a protein without describing the sequence of the protein, and that the reference numbers in a database may change. (Paper 26, p. 2.)

During the interview, Applicants' representatives agreed to amend the sequence listing to add the sequences referred to in the specification by GenBank accession number or depository accession number, solely to advance prosecution. However, upon reconsideration and consultation with PTO personnel, including the Examiner's supervisor, Applicants have decided to traverse this rejection for at least the reasons discussed below.

Applicants need not disclose art-known or standard amino acid sequences or the positions of conserved residues. As the PTO and the courts have stated, what is known in the art need not be disclosed.

At page 57, the specification describes mutations at positions Asp450 and Asp505 in the RNAse H domain of RSV reverse transcriptase. These positions correspond to conserved residues that were described, for example, in Johnson *et al.*, *PNAS USA 83*:7648-7652 (1986) (IDS Document AR9). Johnson *et al.* published an alignment of RSV, M-MLV, HIV and other reverse transcriptase sequences in 1986, which showed that reverse transcriptases have significant conservation between a 150-residue segment in their carboxyl termini (the RNase H domain) and a 250 residue segment in their amino termini (the polymerase domain). *Id.* p. 7649-50, figures 2-4. Johnson *et al.* also pointed out residues that are conserved between the sequences and identified consensus sequences and motifs. *Id.* One of the sequences

aligned in Johnson *et al.* was that of RSV reverse transcriptase. The alignment of the RNAse H domain in Figure 2 of Johnson *et al.* shows both Asp450 and Asp505 of RSV reverse transcriptase, which are marked with asterisks because they are conserved across the aligned sequences. Therefore, the sequence of the RSV reverse transcriptase that was mutanted as described at page 57 need not be disclosed in the sequence listing.

At page 73, the specification makes reference to RSV and AMV reverse transcriptases by their GenBank accession numbers. The GenBank sequences and other reverse transcriptase sequences were known before the priority application date. The complete RSV sequence, for example, was published about 20 years ago. *See* Schwartz, D.E. *et al., Cell 32*:853-869 (1983) (IDS Document AS16). The AMV reverse transcriptase sequence was also known before the priority application date. Therefore, these sequences need not have been included in the specification.

Assuming, arguendo, that changes in a database reference number are even an issue for sequences that have been published, the artisan can search the databases for the sequence at issue by name or organism, rather than by reference number. Therefore, the sequences of the RSV and AMV reverse transcriptases referred to on page 73 by GenBank accession number need not be disclosed in the sequence listing.

Accordingly, withdrawal of the objection is respectfully requested.

Objection to the Claims

The Office Action maintained the objection to claims 148, 150-156, 158-164, 166-175, and 177-182 under 37 CFR § 1.75(d)(1) for allegedly reciting an improper Markush group. (Paper 26, p. 2). Applicants respectfully disagree.

Claims 148, 150-156, 158-164, 166-175, and 177-182 have been canceled, thus rendering moot this basis for objection. By cancellation of these claims, Applicants do not acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter. Withdrawal of the objection is respectfully requested.

The Office Action also maintained the objection to claims 120-124, 126-129, 134, 136-138, 140-143, 150, 158, 166, 177, 184, 198, and 208 under 37 CFR § 1.75(d)(1) for allegedly failing to further limit the subject matter of a previous claim. Office Action, p. 3. According to the Examiner, these claims expand the scope of the claim from which they depend to include mutants and fragments. The basis for this objection is the Examiner's interpretation of the phrase "viral reverse transcriptase." The Examiner states that this phrase can only mean "wild-type enzyme, i.e., isolated from its natural source." (Paper 26, p. 3, lines 29-30). Applicants respectfully disagree.

Claims 122, 127, 136, 141, 150, 158, 166, 177, 184, 198, and 208 have been canceled thus rendering this portion of the objection moot. Claims 120, 121, 123, 124, 126, 128, 129, 134, 137, 138, 140, 142, and 143 relate to a kit or composition comprising two or more viral reverse transcriptases.

Applicants note that the claims are to be interpreted in light of the specification, but limitations from the specification are not read into the claims. *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993) (claims to a superconducting magnet which generates a "uniform magnetic field" were not limited to the degree of magnetic field uniformity required for Nuclear Magnetic Resonance (NMR) imaging. Although the specification disclosed that the claimed magnet may be used in an NMR apparatus, the claims were not so limited).

In the present case, none of the pending independent claims recites the term “wild-type” as alleged by the Examiner. There is no limitation of the scope of the claims to "wild-type" or reverse transcriptase enzyme "isolated from its natural source." Indeed, under the Examiner's interpretation, engineering a mutation in a "viral" reverse transcriptase would transform it into a "non-viral" reverse transcriptase. Applicants respectfully submit that one of ordinary skill in the art would not agree with such an interpretation.

Further, the specification discloses viral reverse transcriptases that may be isolated from sources other than their natural sources. For example, the specification states that reverse transcriptases may be derived from recombinant sources, *i.e.* host cells containing plasmids which produce different reverse transcriptases. Some of these enzymes have mutations, including those that reduce RNase H activity. *See, e.g.*, specification at p. 53-107 and Figures 1-54. Clearly, when the claims are examined in light of the specification and from the perspective of the artisan of ordinary skill, the claims are not limited to "wild-type" viral enzymes as alleged in the Office Action. Therefore, reconsideration and withdrawal of this objection are respectfully requested.

The Rejection Under 35 U.S.C. § 112, First Paragraph Is Traversed

The Office Action, at pages 4-5, maintained the rejection of claims 120, 121, 126-148, 150-156, 158, 159-175, and 177-213 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention. Applicants respectfully traverse this rejection.

Specifically, the Office Action stated that:

> [w]hile the deposited biological materials may overcome an enablement issues [sic], they are no substitute for a proper description of the claimed invention. It is untrue that retroviral sequences are highly conserved. In fact, several known sequences for HIV-1 RT are known in the prior art. Thus, indicating that an amino acid residue number XX of AMV-reverse transcriptase without identifying the sequence may or may not exist in another AMV RT from a different source than that of the applicants. Similarly, the problem would be even further magnified, if the reverse transcriptase is from a different retroviral [sic]. The specification has not identified any sequences of RT that can be used as a standard amino acid sequence for numbering purposes. Also, it has not taught any conserved amino acid residues among all reverse transcriptase or those required for the various activities. The specification merely identify [sic] a single residue(s) from a specific RT without even explaining the structure bases [sic] for such a mutation. Tables 1 and 2 in the specification show increase cDNA produce [sic] upon the addition of other RTs. That would be [sic] support a claim for a composition comprising more than one RT, but the instant claims are directed to RT composition comprising RT's with different pausing sites. Thus, since the Applicants have not taught the various posing [sic] sites, one of ordinary skill in the art would recognize that the applicant[s] were not in position [sic] of the claimed composition at the time the application was filed.

Office Action, p. 4, lines 18-35. Applicants respectfully disagree.

Claims 127, 136, 141, 148, 150-156, 158, 159-175, and 177-213 have been canceled thus rendering moot this portion of the rejection. By the cancellation of these claims, Applicants do not acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter. Claims 120, 121, 126, 128-135, 137-140, and 142-147 relate to a kit or composition comprising two or more viral reverse transcriptases.

The description only needs to describe what is new or not conventional. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d at 1384, 231 USPQ at 94; MPEP 2163, p. 2100-165, col. 2 (Rev. 1, Feb. 2003). The Federal Circuit has also recently clarified that functional descriptions of genetic material may be adequate to meet the written

description requirement if, in the art, that function is correlated with a known structure. *Moba, B.V. v. Diamond Automation, Inc.*, Nos. 01-1063 and 01-1083, 2003 U.S. App. Lexis 6285, at *31-32 (Fed. Cir., Apr. 1, 2003)[1]; *see also, Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.3d. 1313, 1332 (Fed. Cir. 2003) (citing *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 63 U.S.P.Q.2d, 1609 (Fed. Cir. 2002)).

Applicants also note that there are no outstanding enablement rejections in the application. The Federal Circuit recently emphasized that

> In Enzo and Amgen, the record showed that the specification that taught one of ordinary skill in the art to make and use an invention also convinced that artisan that the inventor possessed the invention.

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. Lexis 6285, at *32-33. Therefore, the finding by the PTO that the claims are enabled is further evidence that one of ordinary skill in the art would have recognized that Applicants had possession of the claimed invention.

1. The Deposited Biological Material

Contrary to the statement in the Office Action, Applicants' specific references to the deposited biological materials may meet the written description requirement according to the Court of Appeals for the Federal Circuit and the PTO. As the court recently stated,

> [i]n light of the history of biological deposits for patent purposes, the goals of the patent law, and the practical difficulties of describing unique biological materials in a written description, we hold that reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form, constitutes an adequate written description of the deposited material sufficient to comply with the written description requirement of § 112, ¶ 1.

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Enzo Biochem, Inc. v. Gen-Probe Inc., 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002); *see also,* MPEP 2163, p. 2100-160, col. 1 and p. 2100-165, col. 2 (Rev. 1, Feb. 2002).

Applicants also submit herewith a copy of a Declaration Concerning Deposited Biological Material, filed in related Application No. 09/245,026 on October 22, 2002. Applicants therefore respectfully believe all requirements concerning the deposited material have been met. 37 C.F.R. 1.801-1.809.

2. Reverse Transcriptase Sequences and Alignments

As stated above, numerous reverse transcriptase sequences have been published, such as the nucleotide sequences for M-MLV reverse transcriptase, AMV reverse transcriptase, and HIV reverse transcriptase, as well as mutant sequences. *See, e.g.,* Dudding, L.R. *et al.*, *Biochemistry 30*:10498-10506 (1991) (IDS Document AR4); Messer, L.I. *et al.*, *Virology 146*:146-152 (1985) (IDS Document AS13); Mizrahi, V. *et al.*, *Nucl. Acids Res. 18*:5359-5363 (1990) (IDS Document AR14); Repaske, R. *et al.*, *J. Virology 63*:1460-1464 (1993) (IDS Document AS15); Shinnick *et al.*, *Nature 293*:543-548 (1981)[2]; Joliot *et al.*, *Virology 195*:812-819 (1993)[3]; and Ratner *et al.*, *Nature 313*:277-284 (1985)[4]; Telesnitsky, A. *et al. PNAS USA 90*:1276-1280 (1993) (IDS Document AT18); Kotewicz, M.L., *et al.*, *Nucleic Acids Research 16*:265-277 (1988) (IDS Document AT10); Hizi, A. *et al.*, *Virology 175*:575-580 (1990) (IDS Document AT7); Kotewicz *et al.*, U.S. Patent No. 5,244,797 (1993) (IDS Document AD1); Weiss *et al.*, U.S. Patent No. 4,663,290 (1987) (IDS Document AA1).

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Additional citations will be submitted upon request. As the PTO and the courts have stated, what is known need not be disclosed.

Although not required to comply with the written description requirement, the specification also teaches sequences of specific mutations within subunits of reverse transcriptases. *See, e.g.,* specification, p. 26, line 3; p. 56, line 25 to p. 57, line 12; and p. 73, line 20. The specification also discloses the construction of reverse transcriptase β subunit genes encoding the precursor form or the mature form of the β subunit. *See, e.g.,* specification, p. 56, line 4 to p. 57, line 18; and pp. 90-96. Based on the known sequences of reverse transcriptases and the examples disclosed in the specification, one of ordinary skill could determine that the inventors had possession of the claimed invention.

Further, with regards to a "standard" amino acid sequence and "conserved" residues, Applicants submit these concepts were well known in the art and need not have been disclosed. For example, Johnson *et al.* published an alignment of RSV, M-MLV, HIV and other reverse transcriptase sequences in 1986, which showed that reverse transcriptases have significant conservation between a 150-residue segment in their carboxyl termini (the RNase H domain) and a 250 residue segment in their amino termini (the polymerase domain).[5] Johnson, M.S. *et al. PNAS USA 83*:7648-7652 (1986), p. 7649-50, figures 2-4 (IDS Document AR9). Johnson *et al.* pointed out residues that are conserved between the sequences and identified consensus sequences and motifs. *Id.* One of the motifs Johnson *et al.* identified was the polymerase consensus motif corresponding to positions 337 to 353 of M-MLV reverse transcriptase. Consensus sequences and alignments such as those in Johnson

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[5] The Office Action stated that "[i]t is untrue that retrovial sequences are highly conserved." (Paper 26, p. 4). Applicants respectfully traverse that statement at least as applied to retroviral reverse transcriptases.

et al. establish the corresponding amino acid residues of reverse transcriptases from different viruses. Thus, the specification need not have disclosed a standard sequence or conserved residues because they were known in the art.

Other research published before the present priority date identified numerous residues that are either required or dispensable for various reverse transcriptase activities. Additionally, reverse transcriptase functions correlate with known tertiary structures, as discussed below.

3. Reverse Transcriptase Tertiary Structure

Reverse transcriptases contain a hand domain comprised of fingers, palm, thumb and connection subdomains. *See, e.g.,* Kohlstaedt, L.A. *et al.*, *Science 256*:1783-1790 (1992) and Georgiadis, M.M., *et al.*, *Structure 3*:879-892 (1995).[6] Moreover, Georgiadis *et al.* determined the crystal structure of a proteolytic fragment of M-MLV reverse transcriptase, and compared it to the published crystal structure of HIV reverse transcriptase. They found that the overall fold and structures of the fingers and palm domains in M-MLV and HIV-1 reverse transcriptase are very similar. Georgiadis *et al.*, p. 883, col. 1.

Georgiadis *et al.* found that the fingers domain of M-MLV reverse transcriptase is composed of a highly twisted five-stranded mixed sheet, three α helices, and two β hairpin structures, one of which is part of the sheet. Georgiadis *et al.,* p. 880, col. 2. The palm domain of M-MLV reverse transcriptase is composed of a four-stranded antiparallel β sheet and two long α helices in the core of the domain, a β hairpin in the primer grip region, two short α helices, a short 3_{10} helix, and another short α helix. *Id.*, p. 881, col. 1. The fingers and

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palm domains also contain conserved resides including Lys53, Gln63, Ser195, and Gln260 of M-MLV reverse transcriptase. *Id.*, p. 881, col. 2.

At the junction of the fingers and palm domains lies the polymerase active site. *Id.*, p. 884, col. 1. This site contains three Asp residues (at positions 150, 224 and 225 of M-MLV reverse transcriptase) that are required for polymerase activity. *Id.* The polymerase site in M-MLV reverse transcriptase contains a type II' turn. *Id.*, p. 885, col. 2. HIV-1 reverse transcriptase also contains a type II' turn at the equivalent site. *Id.* In other proteins, position 2 of type II' turns is commonly a Gly residue but in all known wild-type reverse transcriptases, there is a non-Gly residue at this position. *Id.* The residues and interactions that stabilize this structure were also identified. *Id.*, p. 885, col. 2 to p. 886, col. 1.

Georgiadis *et al.* also used the crystal structure of M-MLV and the conserved residues across murine, avian and human reverse transcriptases to identify the structures involved in fidelity, processivity, and selectivity for dNTPs. For example, Georgiadis *et al.* state:

> the highly conserved residues Gln190 (151 in HIV-1 RT) and Gly191 (152 in HIV-1 RT) found in the conserved sequence LPQG within loop β_9-α_H (part of motif B, a conserved sequence found on RTs []), form hydrogen bonds in the minor groove to O2 or N3 of the dNTP and template base, respectively.

Id., p. 886. col. 2. They also state that conserved residues Lys103, Arg 110, and Asp114 interact with the template strand, and Arg116 and Asn119 interact with the primer strand. *Id.*, p. 887, col. 2. With regard to selectivity for dNTPs, Georgiadis *et al.* state that the interaction between the Phe155 and the 2'-hydroxyl of a ribose nucleotide disfavors rNTP, and that Tyr - the only other residue found at that position in reverse transcriptases - would result in the same selectivity as Phe. *Id.*, p. 888, col. 1. Based on the results of Georgiadis *et al.*, Gao *et al.* mutated Phe155 and determined that a substitution with valine allows reverse transcriptase

to incorporate rNTPs. Gao, G. *et al.*, *Proc. Natl. Acad. Sci. USA 94*:407-411 (1997).[7] Clearly, as the evidence above shows, the structure of reverse transcriptases is well defined and highly conserved. Additionally, the polymerase functions of reverse transcriptases correlate with known structures.

4. Pause Sites

With regard to the Office Action's statements about reverse transcriptases having different pause sites, the specification states that the "combination of two or more enzymes having distinct reverse transcription pause sites facilitates production of full-length cDNA molecules since the secondary structural and sequence barriers may be overcome." Specification, p. 34, lines 15-18. Table 2 in the specification exemplifies that using two or more different reverse transcriptases in a transcription reaction did in fact increase the yield of *full length* cDNAs. Specification, p. 68. The Office Action did not specifically address this evidence of an increased yield of *full-length* cDNA.

Further, there is a strong presumption that an application as filed contains an adequate written description of the claimed invention, *In re Wertheim*, 541 F.2d 257, 262 (CCPA 1976) and MPEP 2163, p. 2100-160, col. 2, and the Office Action did not provide any evidence to contradict Applicants' data or conclusions. Consequently, the Examiner has not met the burden of establishing any doubt regarding the correctness of the presumptively accurate statements in the present application. The Federal Circuit has reversed rejections that were made without the USPTO citing references to support its conclusions. *See In re Thrift,* 298 F.3d 1357, 1364 (Fed. Cir. 2002); *In re Lee,* 277 F.3d 1338, 1344-45 (Fed. Cir. 2002).

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With regard to the number of species of reverse transcriptases with different pause sites, Example 3 describes at least eight mixtures of reverse transcriptases, depending on the order in which the reverse transcriptases were added, that resulted in an increased yield of full length cDNA over one reverse transcriptase alone. *See* specification, pp. 64-69. The four reverse transcriptases used in these mixtures represent two of the major groups of retrovirus (ASLV, now known as alpharetrovirus; and MLV-related, now known as gammaretrovirus). *See, e.g.*, Dimcheff, *et al.*, *J. Virology 75*:2002-2009 (2001), p. 2002, col. 1, lines 4-7; The Universal Virus Database of the International Committee on Taxonomy of Viruses, <http://www.ictvdb.iacr.ac.uk/ Ictv/fs_retro.htm>; *and* Fields, *et al.*, Eds., Fundamental Virology, Third Edition, p. 765 (1993).[8] Additionally, the AMV and M-MLV reverse transcriptases, along with HIV reverse transcriptase, have served as models for understanding the structure and function of the entire class of reverse transcriptases. *E.g.,* Prasad V.R., "8. Genetic Analysis of Retroviral Reverse Transcriptase Structure and Function," in: *Reverse Transcriptase*, Skalka, A.M. and Goff, S.P., eds., Cold Spring Harbor Laboratory Press, Plainview, NY, pp. 135-162, at p. 135 (1993) (IDS Document AR15); *see also*, Georgiadis, M.M., *et al., Structure 3*:879-892 (1995) (reporting the crystal structure of a fragment of M-MLV for use as a model for HIV-1 reverse transcriptase, with the ultimate goal of designing more effective drugs against HIV).[9] Thus, Applicants submit that the specification describes a representative number of species within the claimed genus of a combination of reverse transcriptases having different pause sites.

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[9] Copy enclosed herewith for the convenience of the Examiner.

5. βp4 Subunit

Regarding the term "βp4 subunit," Applicants described the βp4 subunit throughout the specification. As the specification says,

> Various forms of the individual subunits of ASLV RT have been cloned and expressed. These include a 98-kDa precursor polypeptide that is normally processed proteolytically to β and a 4-kDa polypeptide removed from the β carboxy end (Alexander, F., *et al., J. Virol. 61*: 534 (1987) and Anderson, D. *et al., Focus 17*:53 (1995)), and the mature β subunit (Weis, J.H. and Salstrom, J.S., U.S. Patent No. 4, 663, 290 (1987); and Soltis, D.A. and Skalka, A.M., *Proc. Nat. Acad. Sci. USA 85*:3372 (1988)).

Specification, p. 4, lines 22-28. The specification also describes the construction of a gene encoding the mature β subunit by inserting a translational stop codon at the "p4" subunit cleavage site. *See,* p. 56, lines 12-14. As Alexander *et al.* proposed, the β subunit is initially synthesized as a larger precursor that is cleaved to produce the smaller mature form and a 4 kD fragment. Alexander, F., *et al., J. Virol. 61*: 534 (1987), p. 540, figure 6 (IDS Document AT1). Thus, based on the specification and the well known structure of the β subunit precursor, one of ordinary skill in the art would understand that the "βp4 subunit" is the precursor that contains the 95 kD mature β subunit and the 4 kD fragment. Additionally, mutations in the βp4 subunit are disclosed, for example, at page 20, line 15 to page 22, line 16; and Examples 1 and 7 (pp. 57, 91-2, and 95). Thus, the specification discloses several species of βp4 subunit, contrary to the position in the Office Action. Further, one of ordinary skill could readily envision numerous βp4 subunits, based, for example, on known reverse transcriptase sequences. Thus, the specification conveys the structure of the βp4 subunit to one of ordinary skill in the art, and the species described in the specification are representative of the genus encompassed by the term.

6. Summary

Based on the teachings of the present specification, the deposits of biological materials, the enabling disclosure, and in light of the knowledge in the art, one of ordinary skill in the art would have concluded that Applicants had described a representative number of species of the claimed genus and had possession of the claimed invention. Applicants therefore respectfully request that this rejection be reconsidered and withdrawn.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Are Traversed

The Office Action, at page 5, maintained the rejection of claims 117-148, 150-156, 158-164, 166-175, and 177-213 under 35 U.S.C. § 112, second paragraph as allegedly being indefinite. Applicants respectfully traverse this rejection.

The Office Action asserts that the phrases "ASLV reverse transcriptase," "specific activity . . . units per milligram," and "one or more subunits" render the claims indefinite. (Paper 26, p. 5). Applicants respectfully disagree.

Claims 122, 127, 136, 141, 148, 150-156, 158-164, 166-175, and 177-213 have been canceled thus rendering moot this basis for the rejection. By cancellation of these claims, Applicants do not acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter. Withdrawal of the rejection is respectfully requested.

1. ASLV Reverse Transcriptase

Concerning the term "Avian Sarcoma-Leukosis Virus (ASLV) reverse transcriptase," Applicants respectfully disagree with the rejection because ASLV is a particular genus of retrovirus, now known as the alpharetrovirus genus. *See, e.g.,* Dimcheff, *et al.*, *J. Virology*

75:2002-2009 (2001), p. 2002, col. 1, lines 4-7[10]. Because the term "ASLV" is an art-recognized term referring to a particular genus of retrovirus, it is clear and definite to the artisan of ordinary skill. Nevertheless, as discussed at the interview, Applicants have canceled this language from the pending claims, merely to expedite prosecution. Accordingly, this portion of the rejection has been rendered moot.

2. One or More Subunits

The Office Action further states that the term "one or more subunits" is indefinite. Applicants have canceled the claims that recite this phrase. Therefore, this portion of the rejection is moot.

3. βp4 Subunit

In addition, the Office Action states that "there is no gene encoding the mature β subunit or 'βp4' subunit which can be processed further to something else. The primary product of the retroviral genome is a polyprotein which is processed primarily to the α-subunit which is further processed to the β-subunit." (Paper 26, p. 6, lines 12-15). Applicants respectfully disagree.

ASLV reverse transcriptases, such as AMV reverse transcriptase or RSV reverse transcriptase, are comprised of subunits formed by post-translational cleavage of the larger precursor β subunit (approximately 98 kD), forming either a mature α subunit (approximately 62 kD) plus an inactive subunit (approximately 36 kD), or forming a mature β subunit (approximately 94 kD) plus an inactive subunit (approximately 4 kD). The mature α and β subunits may then combine to form monomeric, homodimeric or heterodimeric forms of the reverse transcriptase. *See, e.g.*, specification pages 3-5.

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The "βp4 subunit" is the product of a genetic construct of the precursor β subunit coding sequence, which contains the mature β subunit plus the 4 kD inactive subunit. *See* discussion above in response to the rejection under 35 U.S.C. § 112, first paragraph. Therefore, the specification clearly teaches what is a "βp4 subunit," when viewed from the perspective of the artisan of ordinary skill. Applicants therefore respectfully request reconsideration and withdrawal of this portion of the rejection.

4. Reduced and Substantially Reduced

The Office Action, at page 6, states that the terms "reduced" and "substantially reduced" are relative terms that allegedly render the claims indefinite. Applicants respectfully disagree.

Claims 122, 127, 136, and 141 have been canceled rendering moot this portion of the rejection. By the cancellation of these claims, Applicants do not acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter.

Claims 123, 128, 137, and 142 have been amended pursuant to the Examiner's suggestion. (Paper 26, p. 6). Reconsideration and withdrawal of this portion of the rejection are respectfully requested.

The Rejections Under 35 U.S.C. § 102(b) Are Traversed

The Office Action, at pages 6-7, maintained the rejection of claims 148, 150-156, 158-164, 166-171, 175, 177-203, and 207-213 under 35 U.S.C. § 102(b) as allegedly being anticipated by Soltis *et al., Proc. Natl. Acad. Sci. USA 85*:3372-76 (1988) (IDS document AT17), and Yu *et al., J. Biol. Chem. 267*:10888-10896 (1992) (IDS document AR26), and Boehringer Mannheim Biochemicals Products Catalogue, pp. 92-93 (1995) (IDS document

AT19). In addition, the Office Action maintained the rejection of claims 148, 150-156, 158-164, 166-175, and 177-182 under 35 U.S.C. § 102(b) as allegedly being anticipated by Kotewicz *et al.*, U.S. Patent No. 5,244,797 (IDS document AD1) ("the '797 patent"). Applicants respectfully traverse these rejections.

Claims 148, 150-156, 158-164, 166-175, and 177-213 have been canceled thus rendering moot this basis for rejection. By cancellation of these claims, Applicants do not acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter. Withdrawal of these rejections is respectfully requested.

The Rejections Under 35 U.S.C. § 103(a) Are Traversed

The Office Action, at page 8, maintained the rejection of claims 148, 150-156, 158-164, 166-175, and 177-213 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Soltis *et al.* in view of the alleged state of the art at the time the application was filed as exemplified by Chattopadhyay *et al., Prot. Exp. Purification 3:*151-9 (1992) (IDS document AS24).

The Office Action also maintained the rejection of claims 148, 150-156, 158-164, 166-175, and 177-213 under 35 U.S.C. § 103(a) as allegedly being unpatentable over the alleged fact that AMV and M-MLV reverse transcriptases are commercially available from Boehringer Mannheim Biochemicals and U.S. Biochemical in view of the state of the art at the time as exemplified by Chattopadhyay *et al.* Applicants respectfully traverse these rejections.

Claims 148, 150-156, 158-164, 166-175, and 177-213 have been canceled thus rendering moot this basis for rejection. By cancellation of these claims, Applicants do not

acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter. Withdrawal of these rejections is respectfully requested.

The Obviousness-Type Double Patenting Rejections Are Traversed

The Office Action also maintained the rejection of claims 148, 150-156, 158-164, 166-175, and 177-213 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,244,797. The Office Action also maintained the rejection of claims 148, 150-156, 158-164, 166-175, and 177-213 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-84 of U.S. Patent No. 6,063,608. Applicants respectfully traverse these rejections.

Claims 148, 150-156, 158-164, 166-175, and 177-213 have been canceled thus rendering moot this basis for rejection. By cancellation of these claims, Applicants do not acquiesce to the Examiner's position but only wish to expedite the prosecution of allowable subject matter. Withdrawal of these rejections is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and request that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Helene C. Carlson
Helene C. Carlson
Agent for Applicants
Registration No. 47,473

Date: August 11, 2003
1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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